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DOI: https://doi.org/10.1159/000339345

The Opinion Corner

Respiration

Respiration 2012;84:163–175
DOI: 10.1159/000339345

Received: November 24, 2011
Accepted after revision: April 25, 2012
Published online: July 20, 2012

Practical Approach to Emergencies in Lung Transplant Recipients: How We Do It

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Key Words
Lung transplantation · Immunosuppression · Emergency · Respiratory infection · Respiratory symptoms · Reflux · Diagnostics · Therapeutics · Prevention

Abstract
Lung transplant recipients (LTRs) are prone to medical complications and emergencies due to the transplanted organ being in constant direct contact with the environment and the need for life-long profound immunosuppression (IS). As a result of these specific circumstances, the medical and surgical management of LTRs frequently differs from usual standard care. Therefore, we outline here some of the principles we take into account when dealing with the most frequent medical emergencies encountered in our lung transplant cohort in Zurich. The main topics dealt with are: diagnostics and treatment of infections, gastrointestinal emergencies, IS and other medication issues as well as work-up of unclear inflammatory signs and peri-operative precautions in LTRs. Early post-operative transplant complications, rare medical emergencies and surgical problems are not covered. Our report is intended to help internists and pulmonologists new to the field to obtain a better understanding of the peculiarities of LTRs and their management.

Introduction

Complications after lung transplantation have been widely reported, generally including the analysis of aetiological factors [1–7]. Some of these reports mention strategies to prevent these complications. Very few formal guidelines exist for the practical management of lung transplant recipients (LTRs) with the exception of guidelines concerning infectious diseases and immunosuppression (IS) [8–10]. Some single-institution or organisation documents offer comprehensive practical advice [11–13]. Reports on emergency department presentation and care of LTRs are scarce [14–17]. We therefore aim to summarise here some of the frequent emergency situations we encounter in our cohort of LTRs and report on how we deal with these situations. We are aware that medical practice varies strongly, influenced by local conditions. Therefore, this report is merely one possible way to approach these situations and has no claim of being best practice or universally applicable. It may stimulate discussions and research.

The majority of frequently occurring medical emergencies are related to the life-long, mostly triple immunosuppressive therapy and the multiple concomitant drugs resulting in long-term polymedication with several adverse effects and drug interactions requiring a complex

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Table 1. Common reasons for acute lung function deterioration in LTRs

Infection of respiratory tract
Acute allograft rejection with or without visible endobronchial secretions/mucus plugging
Bronchial complications: anastomotic stenosis, malacia
Chest or abdominal pain
Chest wall herniation
Pleural effusion
Intra-abdominal process (ascites, stool retention/coprostasis)
Aspiration (after vomiting)

Lung function here refers primarily to forced expiratory volume in 1 s; however, evolution of forced vital capacity and carbon dioxide transfer factor are considered as well.

medical management approach. The complications most frequently seen are due to infection, graft rejection and other drug-related effects such as bone marrow suppression or skin and bone lesions. For the purpose of our report, we distinguish six groups of emergencies: (1) problems relating to IS, allograft rejection and polymedication; (2) respiratory tract infections and other infectious complications; (3) gastrointestinal emergencies; (4) cardiovascular, renal and fluid balance problems; (5) pain and bone-related problems, and (6) surgery and other invasive procedures. Most health problems in LTRs affect different organs simultaneously, requiring a more complex medical approach. For symptom and problem management purposes, it is advisable to deal with the organ-specific signs and symptoms and focus on immediate resolution without questioning the maintenance IS and concomitant drugs. However, it is important to remember that symptom presentation and severity is frequently blunted by the immunosuppressive therapy [18]. Therefore, preemptive strategies and frequently obtained laboratory results, imaging studies or functional measurements are required to assess the true clinical status of the patient and the response to treatment. The medical emergencies discussed below will be dealt with, not in the order of their frequency or severity, but in the order of the previously listed groups of emergencies related either to the aetiology or the organ system involved.

Practically all LTRs transplanted in Zurich are primarily managed long-term for all health issues by our lung transplant unit, which is part of the division for pulmonary medicine at the University Hospital Zurich. In this setting, internists and pulmonologists in training are also involved, many without any previous contact with transplant medicine. This paper is meant to facilitate an understanding of the principles we respect in the management of LTRs. It is written for these junior doctors and specialists of other fields who collaborate with us to achieve optimal care for these patients by remaining in constant contact with the core care team at the transplant unit. Most of what we do at a practical level has been a result of trial and error over many years and has proven its importance over time without being based on randomised clinical trials. Many practices are not strictly speaking compatible with the highest levels of evidence-based medicine. Until such evidence becomes available, we respect the lower level of evidence or the recommendations based on expert opinion and our experience.

Home Spirometry, Lung Function over Time and Signs of Rejection

A key component for successful allograft and overall patient survival is adequate IS [19]. Inadequate IS triggers acute graft rejection, which is sometimes clinically inapparent or presents with subtle signs and symptoms such as dyspnoea, low-grade fever, cough and malaise [3, 13, 20]. In the early stages of rejection, the only sign may be the lung function deterioration, i.e. reduction in forced expiratory volume in 1 s by >10% from the current baseline or more on two consecutive days or hypoxaemia at rest or with exercise [13]. The definitive diagnosis of allograft dysfunction requires more specific investigations. Often a longer observation period is needed to confirm and classify the rejection and to differentiate between acute and chronic forms [2, 20–22]. In general, patients are instructed to perform home spirometry on a daily basis and are advised to contact the transplant team or physician if the lung function deteriorates [23, 24]. The evaluation of lung function loss and the predominant aetiological aspect requires experience with this complex topic. Some reasons and aetiologies are listed in table 1. Identification and early treatment of suspected or likely acute rejection is the key step in early management of this problem. Technical issues such as a defective home spirometer or a suboptimal spirometry technique have to be excluded. Definitive evaluation must be performed by the lung transplant physician as soon as possible. Anti-rejection treatment is only given if all other causes of allograft dysfunction have been excluded or treated appropriately [3, 13]. This is especially true for a respiratory tract infection, as it may present in a similar way. Clinical assessment and non-invasive evaluations (imaging, lung func-

tion) do not reliably distinguish between infection and rejection [13, 25]. Nevertheless, work-up for possible infection or rejection will include history, clinical examination, lung function tests and a high-resolution computed tomography (HRCT) of the lung (with expiratory images, without using a contrast agent) [13]. A typical pitfall is to rely on a chest radiograph to exclude such a pathology [17]. A chest X-ray may only show features suggestive of advanced stages of rejection (bronchiectasis, pleural effusion) or help detect alternative diagnoses such as cardiac failure [26]. Since the early diagnosis and treatment of infection or rejection is essential, HRCT images are evaluated to make alternative diagnoses and choose the location for biopsy sampling at bronchoscopy, with subsequent sample assessment by a transplant-experienced pathologist [20, 26–28]. HRCT alone is not sufficiently specific and sensitive to reliably diagnose rejection. In acute rejection, HRCT findings may include ground-glass opacities (often with basal distribution), peribronchial cuffing, septal thickening and new or more extensive pleural effusion. In chronic rejection, dilated bronchi, bronchiectasis, mosaic attenuation and air trapping (on expiratory scans, more pronounced in the lower lobes) may be observed [27, 29]. Bronchoscopic biopsies may contribute to the tissue diagnosis of acute rejection [29, 30]. Chronic rejection can be diagnosed based on functional criteria [2, 3, 21, 22], and if tissue diagnosis is sought, then surgical biopsy is more likely to be diagnostic [13].

Immunosuppression

Life-long triple IS is standard after lung transplantation [19]. At our centre, cyclosporine A, mycophenolate mofetil (MMF) and prednisone are predominantly used. Only exceptionally are tacrolimus or everolimus used in our LTRs. Beyond the early transplant phase, the IS is titrated to the lowest acceptable dose of the immunosuppressive drugs that prevents allograft rejection. In this process, the cyclosporine dose is most closely monitored, with measurement of serum drug levels, often termed therapeutic drug monitoring (TDM) [31]. Dose adjustments are required especially when drug regimens are changed and drug interactions occur [2]. The adverse effects of cyclosporine need to be taken into account when the patient's clinical condition deteriorates, for example if the renal function is progressively impaired [2, 32]. As is common practice elsewhere, we taper the steroid dose to a 0.1–0.15 mg/kg/day maintenance dose beyond 12 months after transplantation and additionally aim for a suppressed lymphocyte count as a marker for the therapeutic effect of MMF. In our setting, leucopaenia is most often the dose-limiting factor for MMF dosing. Only as an indicator of compliance and intestinal drug uptake do we occasionally measure MMF drug levels. TDM-oriented dosing of MMF is a debated issue, and data for LTRs are insufficient to strongly support any particular TDM-based strategy [10, 33–35]. We lower the cyclosporine dose during the first year after transplantation under constant monitoring for signs of acute rejection [trough drug levels (C0) approx. 80–160 μg/l and target peak drug levels (C2; 2 h after drug intake) 500–700 μg/l 12 months after transplantation if renal function is normal]. If kidney impairment occurs, reduction of the nephrotoxic immunosuppressive drugs and other drugs is required, aiming for a good allograft function and prevention of further deterioration of renal function [19, 31, 32].

The 'fine-tuning' of IS for each individual patient is a process that occurs over months and years, an integrative process whereby previous laboratory results influence the overall strategy. A 'one strategy fits all' approach is hardly ever possible. Area under the curve measurements for cyclosporine are periodically performed in order to assess drug exposure and drug peak timing and serve to fine-tune the dosing and monitoring parameters (determine for example if C1 or C2 is the best 'peak' time point) [31]. Frequently, multiple dose adjustments are required based on allograft function, pathology results from trans-bronchial biopsies obtained at surveillance bronchoscopy and consideration of interactions with concomitant medications and potential for adverse events. Typically, co-medication with itraconazole influences cyclosporine drug levels as well as the timing and shape of the peak curve. Despite extensive efforts to maintain optimal IS, there are multiple factors that lead to chronic lung allograft dysfunction, with bronchiolitis obliterans syndrome (BOS) being the most common one [22, 36]. BOS, the physiological correlate of histologically proven bronchiolitis obliterans, affects up to 50% of surviving LTRs by 5 years after transplantation [7]. BOS is defined by a >20% decrease in forced expiratory volume in 1 s from the post-transplantation baseline after the exclusion of other causes such as acute airway infection. It is classified into different stages depending on the severity of lung function impairment (BOS grades 1–3) [3, 21, 22]. Causes, mechanisms and therapeutic approaches to BOS are beyond the scope of this article [2–5, 22, 36]. In the case of suspected BOS, expert referral (to a transplant centre) is strongly advised.

Table 2. Typical medication used in the first year after transplantation

Active ingredient	Typical dosage	Main indication/function
Cyclosporine A	Q12H, dose according to TDM	IS
MMF[1]	1.5 g Q12H	IS
Prednisone	5–7.5 mg QD	IS
Itraconazole[1, 2]	100–200 Q12H	antifungal prophylaxis
Valganciclovir[1]	450 mg BID	CMV prophylaxis
Valacyclovir	500 mg BID	herpes virus prophylaxis
Amphotericin B	INHAL 10 mg BID	antifungal prophylaxis
Sulfamethoxazole-trimethoprim[1]	0.5–1 tablet TIW	PJP prophylaxis
Calcium-vitamin D3	1 g QD	osteoporosis prophylaxis
Pantoprazole	40 mg Q12H	PPI/antacid
Esomeprazole[1, 2]/omeprazole[1, 2]	40 mg Q12H	PPI/antacid
Domperidone	10 mg TID AC	prokinetic/anti-reflux
Magnesium	10 mmol TID	supplementation
Ibandronate	IV 3 mg 3-monthly	osteoporosis treatment
Zoledronic acid	IV 5 mg yearly	osteoporosis treatment
Paracetamol	1 g PRN	analgesia
Metamizole	500 mg PRN	analgesia
Macrogol 3350	6–18g/day	laxative

All drugs are taken orally unless stated otherwise. Some dosages may have to be adjusted to underlying or co-morbid conditions such as CF, kidney dysfunction, bone marrow suppression or body weight. QD = Once a day; BID = twice a day; TID = three times a day; Q12H = every 12 h; PRN = as needed; AC = before meals; IV = intravenous route; INHAL = inhalation; TIW = three times a week; PJP = pneumocystis jiroveci pneumonia.

[1] Drug may cause cytopaenia.

[2] Introduction of this drug interacts with cyclosporine metabolism by increasing cyclosporine levels. Both drugs should be given at fixed time points, and for cyclosporine, TDM is recommended.

Intravenous IS and Laboratory Investigations

Since adequate and uninterrupted IS is one of the key features of BOS prevention, all effort must be taken to optimise IS. In situations where oral or enteral (via duodenal or jejunal tube) drug application is either inadequate or not feasible, IS medication has to be given intravenously. We then replace prednisone by methylprednisone (in equipotent doses, i.e. nominally a dose reduction of 20%), give the identical MMF dose intravenously (1:1) and reduce the intravenous cyclosporine dose (given over 4 h) nominally to 1/4 to 1/3 of the oral dose. Close monitoring of the cyclosporine trough level (C0) and kidney function is recommended for this situation.

Because of the complexity of LTRs and the extensive co-medication, routine and emergency laboratory investigations for hospitalised patients and outpatients must cover the following: electrolytes (sodium, potassium, magnesium, phosphate, calcium), kidney function (creatinine, urea), C-reactive protein, liver function, bilirubin, lactate dehydrogenase, creatine kinase, full blood count including differential white blood cell count and cytomegalovirus (CMV)/Epstein-Barr virus (EBV) serum blood counts (PCR) [28, 32]. We aim to verify both cyclosporine trough (C0) and peak levels (C2, or if appropriate C1).

Standard and Special Medication

When more than 15 different drugs are used daily (polymedication) over longer periods of time, then drug interactions (with increased or decreased drug effects) as well as increased drug toxicity or adverse events must be considered. It is advisable to use drugs that have a low potential for drug interaction or drugs with known interaction patterns in the situation of LTRs. We therefore focus on a limited number of drugs with known characteristics when used in polymedicated LTRs. Lists of these frequently used drugs are shown in tables 2 and 3. For every other drug used, the interaction potential and possible adverse events (including the nephrotoxic potential) should be considered prior to its application (table 4). Both calcineurin inhibitors (CNIs), cyclosporine and ta-

Table 3. Add-on medication for specific situations, emergencies or co-morbid conditions

Active ingredient	Typical dosage	Main indication/ function
Ciprofloxacin	500 mg BID	antibiotic
Amoxicillin-clavulanate	1 g BID	antibiotic
Levofloxacin	500 mg QD	antibiotic
Metronidazole[1, 2]	500 mg TID	antibiotic
Meropenem[1]	IV 1 g Q8H	antibiotic
Piperacillin-tazobactam[1]	IV 4.5 g Q8H	antibiotic
Teicoplanin	IV 100–200 mg QD, TDM	antibiotic
Linezolid	600 mg BID	antibiotic
Tobramycin	INHAL or IV 80 mg or IV 150 mg	antibiotic
Colistin	INHAL 1 Mio BID	antibiotic
Caspofungin	IV 50 mg QD	antifungal
Oseltamivir	75 mg BID	antiviral
Vitamin D	300 IU QD	supplementation
Vitamin E	300 mg QD	supplementation
Multivitamins	QD	supplementation
Metoprolol	25–100 mg	anti-hypertensive
Doxazosin mesylate	4–8 mg	anti-hypertensive
Lisinopril	5–20 mg	anti-hypertensive
Clonidine	150–450 mg	anti-hypertensive
NAC	10–20% orally	laxative
Diatrizoate meglumine and diatrizoate sodium	10–50 ml	laxative
Macrogol 4000	0.1–1 litre PRN	laxative
Amiodarone[2]	200 mg QD	anti-arrhythmic
Pravastatin	20–40 mg QD	dyslipidaemia
Amylasum, lipasum, proteasum pancreatis	TID	pancreas enzymes
Ranitidine	150 mg Q12H	antacid
Sertraline	50–75 mg QD	antidepressant
Escitalopram	10 mg QD	antidepressant
Pipamperone	40 mg QD HS	sleep disturbance
Levetiracetam	500 mg Q12H	anti-epileptic
Gabapentin	200–1,200 mg	neuropathic pain
Clarithromycin[2]	125–250 mg Q12H	immunomodulation
Azithromycin	250 mg TIW	immunomodulation
Tacrolimus	Q12H, dose according to TDM	IS
Everolimus	Q12H, dose according to TDM	IS

All drugs are taken orally unless stated otherwise. Some dosages may have to be adjusted to underlying or co-morbid conditions such as CF, kidney dysfunction, bone marrow suppression or body weight. QD = Once a day; BID = twice a day; TID = three times a day; Q8H = every 8 h; Q12H = every 12 h; HS = at bedtime; PRN = as needed; IV = intravenous route; INHAL = inhalation; Mio = million; TIW = three times a week.

[1] Drug may cause cytopaenia.

[2] Introduction of this drug interacts with cyclosporine metabolism by increasing cyclosporine levels. Both drugs should be given at fixed time points, and for cyclosporine, TDM is recommended.

crolimus, have a relevant nephrotoxic effect that must be considered at all times in LTRs. Typically, the cyclosporine dose is affected by a number of drugs with common metabolic pathways in the liver (e.g. clarithromycin or itraconazole), so that introduction of these drugs requires close monitoring of cyclosporine drug levels and adjustment of the dose about 72 h after introducing the new drug (often a dose reduction of cyclosporine by about 1/3 is needed). Use of clarithromycin in LTRs with the current IS regimen is considered dangerous by some trans-

Table 4. Drugs affecting cyclosporine and tacrolimus levels or with nephrotoxic effects

Increase levels of cyclosporine and tacrolimus (leading to toxicity)	
Calcium channel antagonists	diltiazem, verapamil, nicardipine
Antibiotics	erythromycin, clarithromycine, doxycycline
Antifungals	itraconazole, ketoconazole, fluconazole, voriconazole
Gastrointestinal medications	cimetidine, ranitidine, metoclopramide
Other drugs	amiodarone, allopurinol
Decrease levels of cyclosporine and tacrolimus (leading to rejection)	
Antibiotics	nafcillin, sulfamethoxazole-trimethoprim IV, isoniazid, rifampicin
Anticonvulsants	phenytoin, phenobarbital, carbamazepine
Other drugs	*Hypericum perforatum* (St. John's wort)
Increase nephrotoxicity without changing drug levels	
Antifungals/antivirals	amphotericin B, acyclovir, valganciclovir
Antibiotics	aminoglycosides, sulfamethoxazole-trimethoprim p.o.
Non-steroidal anti-inflammatory drugs (all formulations)	
Radiocontrast agents	
Ranitidine	

Modified from Knoop et al. [2] and Playe and Heilpern [15]. IV = Intravenous; p.o. = orally.

plant centres due to the described interaction with the possibility of strongly increasing cyclosporine toxicity [12]. The macrolide azithromycin has a similar bactericidal and immunomodulatory efficacy without pronounced interaction potential and is therefore safer and considered the drug of choice to counteract BOS in LTRs, especially in those with neutrophilic bronchoalveolar lavage (BAL) fluid [3, 22, 37, 38]. Azole-based antifungal treatment is prone to interactions (especially with rifampicin), so that insufficient drug levels may result despite regular intake. These situations require frequent TDM and dose adjustments. In situations of increased risk of invasive fungal infections (augmented IS) or documented fungal infection, we consider treating temporarily with caspofungin, bearing in mind that it does not cover zygomycosis infection [39]. In contrast to guidelines and common practice elsewhere, we hardly ever use fluconazole or voriconazole [40–42].

For reasons of drug interaction stability, the maintenance drugs are taken at fixed intervals and time points (generally 12-hourly together with cyclosporine). Certain proton pump inhibitors (PPIs) also interact with cyclosporine; thus, it is not advisable to switch PPIs unless exceptional reasons exist and close TDM can be performed [39]. For similar reasons, we do not change or permanently stop giving drugs with known interactions, even if a new drug is introduced to treat an intercurrent problem (infection). We accept the transient overlap of treatment. For example, we do not pause itraconazole for reasons of drug interaction balance when we treat a fungal infection with caspofungin intravenously. It also does not make sense to pause azithromycin or clarithromycin given for immunomodulation (not infection) in BOS when another antibiotic is transiently introduced [5]. This is a common pitfall for physicians not familiar with the treatment concepts established for LTRs. The need for accurate pancreas enzyme replacement therapy in cystic fibrosis (CF) patients following lung transplantation requires particular attention; variations in dosing and stool frequency may strongly influence intestinal drug uptake and therefore change drug levels [39]. If insufficient drug levels for IS or antifungal prophylaxis are observed in these patients, intravenous IS and antifungal treatment must be considered in order to prevent allograft rejection or fungal infection [43]. For general physicians without experience in transplant medicine, it is sometime surprising to realise that seemingly 'harmless' drugs might cause serious complications due to non-anticipated interactions and subsequent adverse events (e.g. diclofenac with subsequent renal failure, fluconazole with subsequent increased cyclosporine toxicity).

Cytopaenia

Polymedication and IS very frequently lead to cytopaenia due to bone marrow suppression [5, 13]. Most frequently, leucopaenia, lymphopaenia, neutropaenia and anaemia are observed, and sometimes also thrombocytopaenia. Lymphopaenia is aimed for as part of the immunosuppressive strategy and it is therefore monitored closely (by obtaining the differential white blood cell count) to assess the therapeutic effect of MMF. LTRs are generally treated with more than one drug that tends to cause cytopaenia as an adverse event. This leads to an increased incidence of cytopaenia (generally leucopaenia). When this occurs, the culprit drugs must be reduced (or stopped) immediately in order to allow for recovery from

bone marrow suppression. We primarily reduce (or pause) the following drugs: MMF, valganciclovir, sulfamethoxazole-trimethoprim, metronidazole and intravenous antibiotics (i.e. piperacillin-tazobactam or meropenem). Sometimes the PPI is reduced as well although it very rarely causes cytopaenia. It might be advisable to give alternative drugs such as ranitidine to replace the PPI and to reduce the dose of the intravenous antibiotic. If we pause valganciclovir, we normally start the patient on valacyclovir instead [44]. After recovery from cytopaenia, we reintroduce the drugs carefully. During this period, frequent monitoring of white blood cell counts is mandatory. Similarly, in progressive renal impairment, drug doses have to be adapted accordingly, i.e. sulfamethoxazole-trimethoprim (1/2 tabs), valganciclovir or antibiotic doses need to be reduced, paused or replaced by less nephrotoxic medication.

Approach to Respiratory Tract Infection and Infection of Unclear Origin

Respiratory tract infection is by far the most frequent emergency observed in LTRs [4, 15, 17]. This is mainly due to profound IS and the fact that the transplanted organ remains in constant contact with the environment. Even minor respiratory symptoms such as throat or nose irritation/pain, runny nose, increased sneezing or a slight cough should prompt investigations, as early treatment may be crucial to prevent prolonged illness. We generally perform nasopharyngeal swabs (NPS; obtained nasally if nasal symptoms are prominent, otherwise pharyngeal swabs are taken) for viral and bacteriological examination and then immediately initiate empiric anti-infective therapy with moxifloxacin (1 × 400 mg daily) and in the influenza season additionally oseltamivir (2 × 75 mg, or 1 × 75 mg daily in LTRs with renal impairment) pending NPS results [45]. Many centres have a more restricted use of oseltamivir. It remains to be determined what signs and symptoms in LTRs will justify its beneficial use and also be cost-effective. We avoid macrolides as short-term antibiotic treatment because of drug interactions (table 4). If laboratory results or lung function deterioration suggest more severe infection, we consider the early start of intravenous antibiotic treatment. In elderly patients with co-morbidities or signs of more severe infection, we prefer hospital admission for inpatient treatment and work-up. If viral NPS results return negative, we stop oseltamivir immediately and generally stop the empiric moxifloxacin treatment after 1 week. If symptoms and/or lung function deterioration persist or inflammatory signs are unexplained, we obtain additional samples from the respiratory tract (sputum if available), and we consider performing a bronchoscopy for additional sampling and even trans-bronchial biopsies if the situation remains unclear [9]. The NPS and BAL fluid analysis includes general bacteriology and mycology (direct stains, culture and drug sensitivity testing) as well as virological investigations by PCR for the following viruses: adenovirus, enterovirus, influenza A and B (including H1N1), parainfluenza, respiratory syncytial virus A and B (RSV) and rhinovirus [28, 46]. Recently, we added coronavirus to this panel, as it is frequently detected in LTRs [47]. Depending on the clinical and radiological findings, we additionally send BAL and/or bronchial washes for detection of CMV, herpes simplex virus, varicella zoster virus, *Nocardia, Legionella, Pneumocystis jiroveci* and *Mycobacteria* [45, 46, 48, 49]. In documented respiratory syncytial virus infection and sometimes in prolonged parainfluenza virus infection, we start oral ribavirin therapy and monitor virus elimination as well as adverse events (typically anaemia) [50, 51]. Fungal infections are common in LTRs and sometimes occur despite apparently adequate antifungal prophylaxis. In the work-up of severe deterioration of pulmonary function, HRCT imaging and bronchoscopic sampling are required for the diagnosis of allograft rejection or infection, for example invasive fungal infection [26–29, 52]. When additional antifungal treatment is required, we prefer caspofungin due to its favourable safety profile. We thereby bear in mind the fungal infections not covered effectively by caspofungin such as zygomycosis, cryptococcosis and *Geotrichum* [53].

In situations of an unclear infectious focus and/or unexplained inflammatory signs in laboratory results (elevated white blood cell count, C-reactive protein or sedimentation rate), infection and rejection must be considered. A good rule of thumb is to consider infection high in the differential diagnosis of any new sign or symptom in LTRs [28]. We undertake a general diagnostic work-up consisting of additional laboratory investigations such as quantitative serum CMV and EBV viral load (by PCR), sampling of NPS (see above), removal (or replacement) of intravenous lines and culture of the catheter tip as well as urine and stool cultures including the detection of *Clostridium difficile* and its toxins [45]. Depending on the situation, additional investigations may be ordered such as blood cultures and sputum culture (including mycobacteria), abdominal X-ray, CT of the thorax and abdomen and sonography of the abdomen or pleura. Bloodstream

infection must be considered even in the afebrile LTR [16]. We always ask for CT scans without intravenous contrast agent due to the substantially increased risk of renal failure in LTRs. CMV and EBV reactivation must always be considered in such situations, so quantitative viral load measurements are requested. CMV reactivation in the first year after transplantation is common and may occur despite adequate prophylaxis under specific circumstances [8, 54, 55]. CMV pneumonia is a feared complication as it is a risk factor for BOS development [22]. Knowledge of the incidence and timing of various types of infection and the responsible pathogens should help in the prevention, early detection and initiation of therapy in LTRs [56–58]. Multiresistant bacteria are frequently encountered in end-stage lung disease, and frequently these bacteria persist in the airways after transplantation (e.g. *Pseudomonas aeruginosa*). Antimicrobial treatment must take into account the presence of these organisms [40, 46, 53].

Empiric infection treatment for early or minor symptoms of respiratory or unlocalised infection would usually include oseltamivir (in the influenza season) and either moxifloxacin or amoxicillin-clavulanate or ciprofloxacin, depending on the suspected organism or previously detected bacteria. If there is any doubt, we generally prefer the application of intravenous antibiotics, i.e. empirical piperacillin-tazobactam to treat Gram-negative pathogens and the addition of teicoplanin in a suspected bloodstream infection to treat Gram-positive pathogens. Rarely do we use vancomycin, the drug of choice for this situation according to the guidelines [45]. In the case of recent antibiotic treatment, we consider *C. difficile* as responsible for gastrointestinal infection and add metronidazole empirically. We have a low threshold to add intravenous antifungal treatment (i.e. caspofungin) to the treatment regimen, in particular if previous sampling is suggestive of a fungal airway infection [52, 53, 59].

If LTRs suffer from frequent episodes of infections, hypogammaglobulinaemia (often due to immunosuppressive therapy) needs to be detected by requesting measurement of immunoglobulin G levels. If the immunoglobulin G level is found to be below the normal range (<7.3 g/l), we give intravenous immunoglobulins to enhance the body's immune defence against infections. This is especially important in documented CMV disease, infection with encapsulated bacteria (e.g. *Klebsiella*) and some viral infections [46, 55]. In suspected infection, we initially reduce the MMF dose by 1/3 to 1/2 of the maintenance dose depending on the severity of the expected infection and the net IS of the patient. Some centres temporarily interrupt MMF therapy at the onset of suspected infection.

Gastrointestinal Tract Emergencies

After respiratory tract infections, gastrointestinal problems are the second most frequent emergency situation in our LTRs [5, 60, 61]. The underlying diagnosis (e.g. CF) may contribute substantially to this, but these emergencies are observed in all patient groups and are partly related to the polymedication leading to decreased gastrointestinal motility and increased food transit time. Intra-abdominal complications strongly affect survival rates in LTRs [60]. Profound IS hampers the diagnosis of many complications by blunting symptoms [18]. This is especially true for abdominal emergencies.

Among the most frequent problems observed in LTRs are obstipation and intestinal obstruction. They are therefore frequently discussed at routine outpatient and emergency visits. Abdominal X-rays are very useful for unclear vomiting, abdominal pain or suspected obstipation as the latter is not always easily diagnosed on clinical grounds. Imaging of stool retention also helps convince patients that consequent treatment is required. Intestinal motility is decreased and gastrointestinal transit is reduced by the standard medication so that laxative treatment is generally needed to loosen stool consistency and allow for regular daily stools. Some patients require combinations of laxatives, including agents used for bowel preparation. This is especially important in distal intestinal obstruction syndrome, a condition typically observed in CF patients [62]. For this syndrome, we also give highly concentrated N-acetylcysteine (NAC) orally (generally 1 ampoule/vial of NAC 10%/20% in orange juice) and/or as an enema (4 vials of NAC 20% in 500 ml of NaCl 0.9%) in order to re-establish intestinal passage. NAC reduces stool consistency. Early aggressive medical therapy is indicated to prevent worsening of the clinical condition and possibly surgical intervention as the ultimate treatment option (enterotomy and faecal disimpaction). Physicians and LTRs alike generally underestimate the potential dangers of unresolved obstipation.

Vomiting within 1 h of taking immunosuppressive medication may severely affect the systemic levels of IS. Therefore, patients are instructed to take the immunosuppressants a second time if this occurs and call the transplant team for advice. Vomiting may be related to insufficient or inverse upper gastrointestinal motility but

can also be a consequence of gastroparesis, decreased lower intestinal motility or bowel obstruction. Vomiting may lead to micro- or even macroaspiration, which is likely to contribute to the development of allograft rejection [37, 63]. Treatment of vomiting is guided by the potential causes. However, symptomatic treatment is initiated early in order to prevent drug malabsorption and aspiration. Frequently, various anti-emetics are tried until a full response to treatment is achieved. In prolonged vomiting refractory to most interventions and other situations where oral uptake is transiently not possible, we have a post-pyloric tube inserted by the gastroenterologist so that medication and feeds can be given intestinally. Nasogastric tubes are very rarely used, exclusively to evacuate gastric contents in initially unclear cases.

Diarrhoea is very frequent, sometimes as a result of the medication (magnesium, MMF or laxatives), but it may have more sinister causes such as *C. difficile,* norovirus or parasitic intestinal infection. Therefore, we maintain a low threshold for performing stool analysis, especially to rule out clostridial infection. For patients with recurrent clostridial infections or high suspicion of antibiotic-associated diarrhoea, we preemptively treat with oral metronidazole pending stool analysis results [45]. Treatment focuses on likely causes and very rarely includes symptomatic treatment with anti-diarrheal medication. No preparations containing *Saccharomyces boulardii* or other probiotics are used at any time. Paradoxical diarrhoea is more frequently seen in LTRs, sometimes even associated with vomiting. Frequently, it is difficult to convince patients (and doctors) of the fact that constipation or distal intestinal obstruction syndrome is present and consequent laxative treatment is needed despite the patient passing loose stools. Abdominal X-rays are very helpful in these situations to demonstrate stool accumulation, exclude other intra-abdominal pathologies (free air?) and prompt patients to use laxative medication consequently.

Rigorous fluid substitution is mandatory during episodes of vomiting and diarrhoea. Close monitoring of drug levels is recommended, since drug absorption is frequently altered by these conditions.

Abdominal pain and other signs and symptoms of intestinal dysfunction are much less frequently observed than in non-transplant patients, even in the presence of severe intra-abdominal pathology. This is due to the blunting of symptoms by IS [18]. If pain occurs, it potentially indicates a more advanced stage of intestinal problem. We maintain a low threshold for urine culture because typical symptoms of urinary tract infection are rare in LTRs, for men and women alike. We perform abdominal or renal ultrasound as our second-line investigation. Causes of abdominal pain are frequently bowel obstruction, colitis of various aetiologies (CMV, *C. difficile,* diverticulitis) and colon perforation. Less often cholecystolithiasis, biliary tract disease or pancreatitis are diagnosed [60, 61, 64, 65].

Gastro-oesophageal reflux (GOR) is very common among LTRs for a number of reasons (e.g. altered thoracic mechanics, effects of immunosuppressive drugs on lower oesophageal sphincter function, vagal nerve dysfunction following surgery and possibly an underlying diagnosis, e.g. scleroderma) [60]. We therefore promote anti-reflux measures for all LTRs, i.e. entire bed with elevated head-end, avoiding lying down within 2 h of eating and drinking, and avoiding known promoters of GOR such as alcohol and caffeine-containing beverages in the evening. In addition, all our patients receive anti-GOR medication (i.e. domperidone, PPI, sometimes ranitidine). Weight reduction and preventive measures during surgical procedures are further important measures to prevent aspiration episodes and their negative consequences on long-term allograft survival. For our LTR cohort, we do not generally perform anti-GOR surgery (fundoplication), even though such an approach has been advocated by other lung transplant programs [66].

Pain and Bone-Related Problems

Since osteoporosis or osteopaenia is common among LTRs, even in young patients, they receive appropriate treatment with daily calcium and vitamin D3 supplements [67]. Most LTRs also receive a bisphosphonate. Despite these measures, fractures occur even after minor trauma. Any pain that may be related to the skeletal system is investigated with X-ray imaging, and if this is inconclusive, we perform MRI or CT scanning, whatever appears more appropriate. We encourage physical exercise such as walking and cycling or the use of the home trainer. We quite often investigate the onset of foot pain and find a metatarsal fracture. Conservative treatment for fractures is attempted in most cases, and prolonged bone healing is anticipated.

Pain in the Achilles tendon, or achillodynia, is sometimes seen in patients on long-term treatment with quinolones (e.g. ciprofloxacin). If the quinolone is not discontinued at an early stage it may lead to partial or complete rupture of the Achilles tendon. In these LTRs, quinolones should be avoided by all means in future antibiotic treatments.

Treatment of pain in the presence of nephrotoxic drugs is a challenge, since we aim to preserve renal function as well as intestinal motility. Usually analgesia is obtained with paracetamol and metamizole or a combination of the two, whereby maximal dosing may be necessary. Only very exceptionally do we use opioids, such as tramadol or fentanyl, due to the frequent adverse effects on intestinal function and the loss of aerodigestive reflexes. Non-steroidal anti-inflammatory drugs are not used in LTRs due to the potential detrimental effects on renal function [32]. We treat localised pain with lidocaine patches, and in rare cases of refractory pain, we additionally use antidepressants or a neuroleptic drug (e.g. gabapentin).

In the case of a minor superficial trauma or lesions to the skin or mucosa (e.g. dental work), we recommend prophylactic treatment with amoxicillin-clavulanate (3 g 1 h prior to a dental procedure and 1 g 3 h thereafter) or giving the drug at the normal dose for 1 week starting 24 h before any minor intervention (e.g. skin biopsy) or after any kind of minor accidental skin lesion (antibiotic prophylaxis) [68–70]. The best prophylactic antibiotic strategy in LTRs remains to be determined.

Cardiovascular and Fluid Balance Emergencies

Arterial hypertension is increasingly observed the longer the interval following transplantation and the older the LTR [5, 7, 71]. A hypertensive crisis may be considered a medical emergency and requires intervention. We tend to accept slightly higher blood pressures than generally recommended for non-transplanted patients, particularly in LTRs with known orthostatic dysregulation, as they are otherwise prone to falls. We generally recommend obtaining blood pressure measurements exclusively in the sitting position and adjusting anti-hypertensive medication based on these measurements only. This needs to be emphasised in hospitalised LTRs in order to prevent orthostatic hypotension and its consequences. We limit anti-hypertensive drugs to a number of known drugs with reduced interaction and adverse event potential (table 3). Calcium antagonists such as amlodipine tend to cause oedema and orthostatic hypotension in our LTRs, so we tend to avoid this additional problem by using other anti-hypertensive drugs. Signs and symptoms of coronary heart disease and heart failure may be masked, and therefore LTRs may be oligosymptomatic despite advanced cardiac/coronary heart disease. With increasing age and survival, detection of relevant cardiovascular morbidity requires respective investigations whereby the less invasive procedures are preferred. Pulmonary embolus should be considered in LTRs with unexplained pulmonary symptoms or evidence of thromboembolic events such as deep vein thrombosis in the extremities (on duplex sonography). We prefer scintigraphic evaluations and avoid contrasted CT scans in order to preserve kidney function.

With regard to fluid balance, oedema and heart failure management, diuretics may be part of the anti-hypertensive regimen, but the hydration status must be considered in all LTRs since overly aggressive diuretic treatment may enhance renal failure due to a pre-renal component, more so than in non-transplanted patients [72]. We tend to encourage our patients to drink sufficient liquids on a regular basis (depending on age and co-morbidity, the amount is individually defined between 2 and 4 litres/day) and adjust diuretics and anti-hypertensive and heart failure drugs to the steady state obtained in a constant hydration status. In this context, daily weight measurement and consideration of drug adjustments is essential. Reduced oncotic pressure may contribute to these problems with loss of fluids into the third space. We generally investigate for renal protein losses when other more obvious causes have been ruled out. Renal loss of magnesium is increased with CNI use (cyclosporine or tacrolimus), thus necessitating sufficient magnesium supplementation for all patients.

Dyslipidaemia is a common problem in LTRs and a known adverse effect of CNI treatment. Pravastatin is the drug with the smallest interaction potential in this context and is therefore the drug of our choice. Long-term cardiovascular complications are seen especially in long-term survivors and influence overall survival [5].

Surgery and Other Invasive Procedures

Surgical interventions go along with an inherent increased risk of complications, which in our experience is substantially increased when compared to non-transplant patients. Intra-abdominal problems in LTRs requiring surgical intervention are associated with a relevantly increased mortality [60]. This is well documented for emergent surgery and/or surgery involving septic complications [60, 65]. Any kind of surgical intervention should therefore be prepared well in advance, particularly in elective cases. The most frequent complications we observe are peri-operative deterioration due to a combination of fluid imbalance/hypertensive blood pressure

Table 5. 'Seven sins' relating to invasive procedures in LTRs

1. Wrong indication or dismissal of conservative strategy. Invasive interventions in situations that may have possibly resolved with consequent conservative measures ('using standard indications for non-standard patients!').
2. Lack of meticulous preparation of procedure involving all possible specialists that may be of relevance (including lung transplant specialist, anaesthetist, experienced surgeon familiar with high complication rate of this population, experienced intensivist for post-operative care) [18, 70].
3. Lack of intravenous anti-infective treatment for at least 2–3 days before and after the surgical intervention (in collaboration with lung transplant specialist).
4. Lack of early and consequent laxative treatment to prevent intestinal complications. Avoid opioids for this reason.
5. Lack of cautious blood pressure control and fluid management; lack of experience with technicalities and pitfalls of blood pressure measurement and control in this population can severely complicate any intervention (arterial hypertension is highly prevalent among LTRs, and many require multiple anti-hypertensives for adequate blood pressure control). Fluid intake should not be restricted pre-operatively to avoid haemodynamic instability and renal dysfunction. Fluid overload should be avoided intra-operatively due to impaired lymphatic drainage [32, 72, 73].
6. Lack of strict anti-reflux measures to prevent GOR and aspiration, such as positioning the patient in the 'tilt position' (reverse Trendelenburg position) at all times irrespective of circumstances, and no enteral feeds via the gastric tube (duodenal or jejunal tube feeding only) [32, 73].
7. Non-anticipation of possible complications (kidney failure due to contrast agent or non-steroidal anti-rheumatics) and failure to implement preventive strategies including having an intensive care unit bed on 'stand-by' for all LTRs post-operatively [72].
This list is applicable to any kind of management procedure relating to LTRs but is specifically true when invasive procedures are anticipated.

measurements and attempts to correct these with subsequent worsening renal function and sometimes acute heart failure. This is likely related to the disruption of pulmonary lymphatics and bronchial circulation leading to an increased risk of pulmonary oedema [72, 73]. Therefore, fluid management should be conservative in the peri-operative setting, and diuretics should be prescribed if necessary [70]. GOR with microaspiration, pulmonary and non-pulmonary infections, wound healing problems, excessive bleeding, intestinal obstruction and need for re-operation are quite common, even in the hands of very experienced surgeons and anaesthetists. If possible, we prefer primarily conservative strategies rather than a surgical intervention and draw attention to the pitfalls by communicating the 'seven sins list' (table 5) to surgical and anaesthetic colleagues when surgical intervention is inevitable. We assist in the planning of surgery and management of our LTRs when surgery appears to be the only feasible solution, including advice on peri-operative antibiotics, securing an intensive care unit bed for post-operative care and engaging an anaesthetist who is familiar with the potential complications of LTRs undergoing surgery [32, 72, 73]. Most of these precautions are respected no matter how small the intervention may appear. Close interaction with the transplant team is likely the single most important step in preparing the transplanted patient for surgery and successfully managing their post-operative care [70].

In summary, LTRs react somewhat differently to a number of external influences including infections, medication and diagnostic or therapeutic interventions. These patients may present in emergency situations with strikingly few symptoms. These aspects require an experienced team for patient management since complications are more common in these frequently healthy-looking patients. We believe our paper draws attention to some of the pitfalls and possible strategies to prevent common complications in LTRs and thus may contribute to better understanding and treatment of LTRs.

Acknowledgements

We would like to thank the pulmonary fellows Bruno Isenring, Jean-Luc Kurzen and Stephan Keusch as well as the reviewers for the critical review of the manuscript.

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